09/762320

PCT/SE00/02263

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 31 July 2001 (31.07.01)	
International application No. PCT/SE00/02263	**Applicant's or agent's file reference** A2272-1 WO
International filing date (day/month/year) 16 November 2000 (16.11.00)	**Priority date** (day/month/year) 22 November 1999 (22.11.99)
Applicant PAGE, Patrick	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

22 May 2001 (22.05.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Charlotte ENGER
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

SE0002263

09/762320

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
A2272-1 WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SE00/02263	16.11.2000	22.11.1999
International Patent Classification (IPC) or national classification and IPC7		
B 01 J 19/00, C 07 C 265/08		
Applicant		
AstraZeneca AB et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 3 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 7 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22.05.2001	14.03.2002
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Telex 17978 PATOREG-S Facsimile No. 08-667 72 88	Authorized officer Monika Bohlin/Els Telephone No. 08-782 25 00

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE00/02263

I. Basis f the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:
pages 1-23 , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

☒ the claims:
pages _____ , as originally filed
pages _____ , as amended (together with any statement) under article 19
pages _____ , filed with the demand
pages 1-7 , filed with the letter of 23.01.2002

☐ the drawings:
pages _____ , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

☐ the sequence listing part of the description:
pages _____ , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheet/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2 (c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item I and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE00/02263

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-15	YES
	Claims		NO
Inventive step (IS)	Claims	1-15	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-15	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

This International Preliminary Examination Report is based on the amended claims 1-15 filed with the letter of 23.01.2002

Documents cited in the International Search Report:

1. Chem. Ber., Volume 111, 1978, page 3965 - page 3968
2. Tetrahedron Letters, Volume 38, No 3, 1997, page 359 - page 362
3. Tetrahedron Letters, Volume 39, 1998, page 7227 - page 7230
4. Tetrahedron Letters, Volume 39, 1998, page 1113 - page 1116
5. Int. J. Peptide Protein Res., Volume 36, 1990, page 182 - page 187
6. US 4812532 A
7. WO 9925752 A1

The cited documents represent the general state of the art.

The invention defined in claims 1-15 is not disclosed by any of these documents.

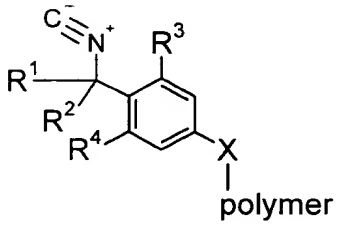
The cited prior art does not give any indication that would lead a person skilled in the art to the claimed functionalised polymeric reagent comprising a linker with an acid labile isonitrile moiety cleavable at the CN-functionality. Therefore, the claimed invention is not obvious to a person skilled in the art.

Accordingly, the invention defined in claims 1- 15 is novel and is considered to involve an inventive step. The invention is industrially applicable.

CLAIMS

1. A functionalized polymeric reagent for solution and solid-phase synthesis comprising a polymer and a linker moiety characterized in that the linker comprises an acid labile isonitrile moiety cleavable at the CN-functionality.

2. A functionalized polymeric reagent for solution and solid-phase synthesis of Formula I



(I)

wherein

X is carbon, oxygen, a PEG-chain, or a $-(CH_2)_n$-CONH- group,

R^1 is hydrogen, phenyl, or substituted phenyl group,

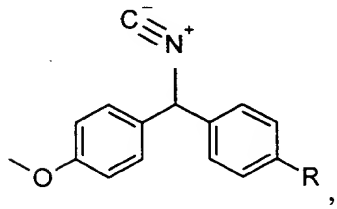
R^2 is hydrogen, phenyl, or substituted phenyl group,

R^3 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or phenoxy,

R^4 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or phenoxy, and

n is an integer from 1 to 4.

3. The functionalized polymeric reagent according to claims 1 or 2 being,



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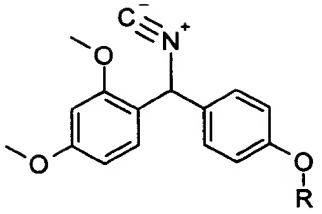
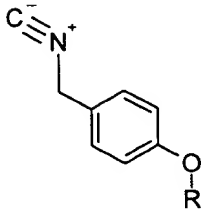
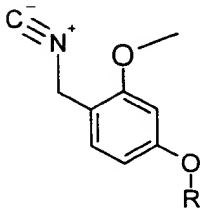
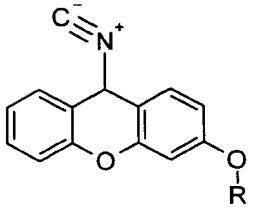
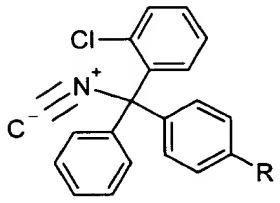










wherein R is a polymer directly attached to the linker or through a $-(CH_2)_n$-CONH- group,or a PEG-chain.

4. The functionalized polymeric reagent according to any of claims 1-3, characterized in that the polymer is a soluble polymer.

5. The functionalized polymeric reagent according to any of claims 1-3, characterized in that the polymer is an insoluble polymer.

6. A method for preparing a functionalized polymeric reagent according to claims 1-5, comprising the step of,
   a) reacting the polymeric support with a formylating reagent;
   b) converting the thereby formed formamido group into an isonitrile moiety.

7. The method according to claim 6, characterized in that the formylating reagent used in step a) is 2,4,5-trichlorophenyl formate.

8. The method according to claim 6 and 7, characterized in that the reagent used in step b) is carbon tetrachloride / triphenylphosphine in the presence of triethylamine.

9. A method for preparing an organic compound by solution and solid-phase synthesis comprising the steps of
   a) immobilizing a substrate compound to the isonitrile moiety of the functionalized polymeric reagent according to claims 1-4
   b) performing at least one further reaction step, and
   c) cleaving the compound from the polymeric support by acid treatment.

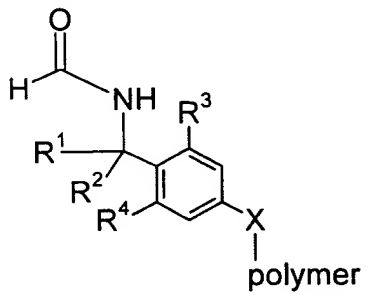
10. The method according to claim 9 comprising an additional reaction step after the cleavage from the polymeric support.

11. The method according to claim 9, characterized in that the method is performed with a plurality of substrate compounds and/or plurality of further reaction steps to give a library of organic compounds.

12. The method according to claim 9, characterized in that at least one of the reaction steps is a multicomponent reaction.

13. A kit comprising a container of a functionalized polymeric reagent according to claims 1-4.

14. Intermediate compounds of Formula II



(II)

wherein

X is carbon, oxygen, a PEG-chain, or a $-(CH_2)_n$-CONH- group,

R^1 is hydrogen, phenyl, or substituted phenyl group,

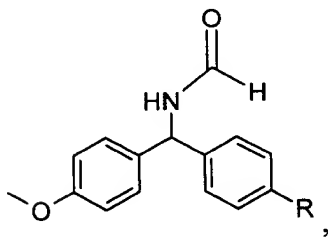
R^2 is hydrogen, phenyl, or substituted phenyl group,

R^3 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or phenoxy,

R^4 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or phenoxy, and

n is an integer from 1 to 4.

15. Compounds according to claim 13 being



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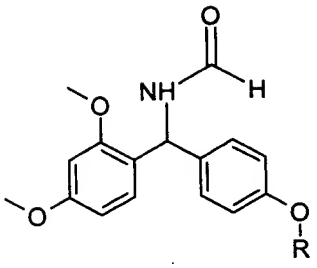

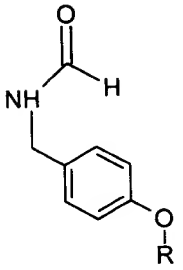

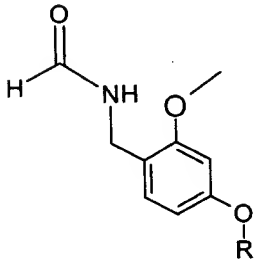

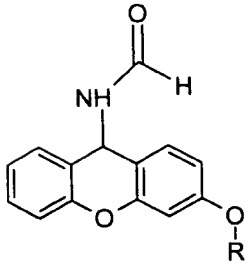

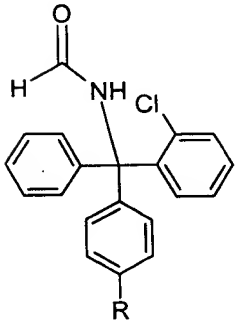

wherein, R represents the polymeric support either directly attached to the linker or through a spacer moiety, such as a PEG-chain or a $-(CH_2)_n$-CONH- group.

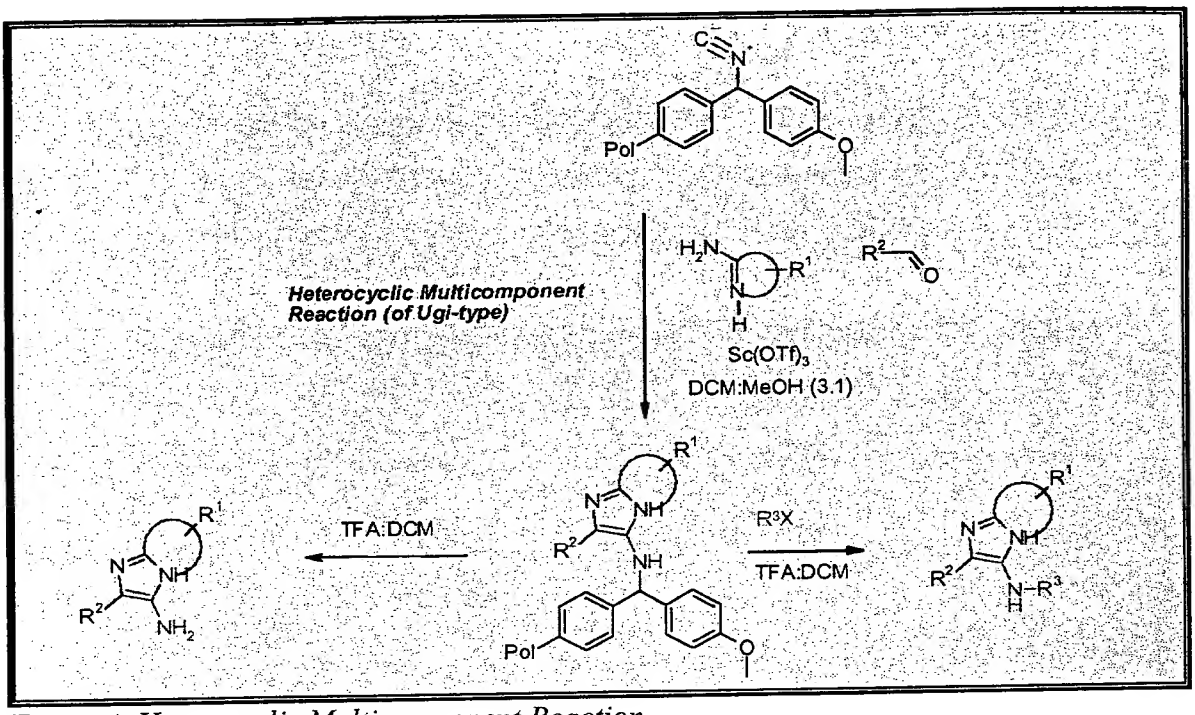

Figure 4. Heterocyclic Multicomponent Reaction

The preferred embodiment shown in Figure 4 is advantageous since it allows a multicomponent reaction to be performed directly onto the acid labile isonitrile moiety of the functionalized polymeric reagent.

The example outlined above consists of a multicomponent Ugi-type condensation wherein the isonitrile moiety of the functionalized polymeric reagent is reacted with 2 different source of diversity, aldehydes and heteroaromatic amidines. This Ugi-type reaction leads efficiently and in a one step process to the fused 3-aminoimidazoles, using the resin capture strategy. The final compounds are of high purity after acid cleavage.

3-aminoimidazoles has been synthesized according to the present invention. A wide range of aldehydes and heteroaromatic amidines was utilised to test the functionalized polymeric reagent and showed the efficiency of the resin capture by obtaining a high yield and excellent purity of the final products. Typical procedure for the synthesis of fused 3-aminoimidazoles by Ugi type reaction and resin capture strategy is described in Example 3, below.

CLAIMS (with amendment in handwriting)

1. A functionalized polymeric reagent for solution and solid-phase synthesis comprising a polymer and a linker moiety characterized in that the linker comprises an acid labile isonitrile moiety cleavable at the CN-functionality.

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* A2272-1 WO

Box No. I TITLE OF INVENTION

NEW FUNCTIONALIZED POLYMERIC REAGENTS

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

AstraZeneca AB
S-151 85 Södertälje
Sweden

☐ This person is also inventor.

Telephone No.
+8 553 260 00

Facsimile No.
+8 553 288 20

Teleprinter No.

State *(that is, country)* of nationality:
SE

State *(that is, country)* of residence:
SE

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

PAGE, Patrick
AstraZeneca R&D Mölndal
S-431 83 Mölndal
Sweden

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:
FR

State *(that is, country)* of residence:
SE

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Global Intellectual Property, Patents
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S-151 85 Södertälje
Sweden

Telephone No.
+46 8 553 260 00

Facsimile No.
+46 8 553 288 20

Teleprinter No.

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

☒ **AP** **ARIPO Patent:** **GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **MZ** Mozambique, **SD** Sudan, **SL** Sierra Leone, **SZ** Swaziland, **TZ** United Republic of Tanzania, **UG** Uganda, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT

☒ **EA** **Eurasian Patent:** **AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakhstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

☒ **EP** **European Patent:** **AT** Austria, **BE** Belgium, **CH and LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☒ **OA** **OAPI Patent:** **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **GW** Guinea-Bissau, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

☒ **AE** United Arab Emirates
☒ **AG** Antigua and Barbuda
☒ **AL** Albania .....
☒ **AM** Armenia .....
☒ **AT** Austria .....
☒ **AU** Australia .....
☒ **AZ** Azerbaijan
☒ **BA** Bosnia and Herzegovina .....
☒ **BB** Barbados
☒ **BG** Bulgaria .....
☒ **BR** Brazil .....
☒ **BY** Belarus .....
☒ **BZ** Belize
☒ **CA** Canada
☒ **CH and LI** Switzerland and Liechtenstein
☒ **CN** China .....
☒ **CR** Costa Rica .....
☒ **CU** Cuba .....
☒ **CZ** Czech Republic .....
☒ **DE** Germany .....
☒ **DK** Denmark .....
☒ **DM** Dominica
☒ **DZ** Algeria .....
☒ **EE** Estonia .....
☒ **ES** Spain .....
☒ **FI** Finland .....
☒ **GB** United Kingdom
☒ **GD** Grenada
☒ **GE** Georgia .....
☒ **GH** Ghana .....
☒ **GM** Gambia
☒ **HR** Croatia .....
☒ **HU** Hungary .....
☒ **ID** Indonesia
☒ **IL** Israel .....
☒ **IN** India .....
☒ **IS** Iceland
☒ **JP** Japan .....
☒ **KE** Kenya .....
☒ **KG** Kyrgyzstan .....
☒ **KP** Democratic People's Republic of Korea .....
☒ **KR** Republic of Korea .....
☒ **KZ** Kazakhstan .....
☒ **LC** Saint Lucia
☒ **LK** Sri Lanka
☒ **LR** Liberia
☒ **LS** Lesotho .....
☒ **LT** Lithuania
☒ **LU** Luxembourg
☒ **LV** Latvia
☒ **MA** Morocco .....
☒ **MD** Republic of Moldova .....
☒ **MG** Madagascar .....
☒ **MK** The former Yugoslav Republic of Macedonia .....
☒ **MN** Mongolia
☒ **MW** Malawi .....
☒ **MX** Mexico .....
☒ **MZ** Mozambique
☒ **NO** Norway
☒ **NZ** New Zealand .....
☒ **PL** Poland .....
☒ **PT** Portugal .....
☒ **RO** Romania
☒ **RU** Russian Federation .....
☒ **SD** Sudan
☒ **SE** Sweden
☒ **SG** Singapore
☒ **SI** Slovenia .....
☒ **SK** Slovakia .....
☒ **SL** Sierra Leone .....
☒ **TJ** Tajikistan .....
☒ **TM** Turkmenistan .....
☒ **TR** Turkey .....
☒ **TT** Trinidad and Tobago .....
☒ **TZ** United Republic of Tanzania
☒ **UA** Ukraine .....
☒ **UG** Uganda .....
☒ **US** United States of America .....
☒ **UZ** Uzbekistan .....
☒ **VN** Viet Nam .....
☒ **YU** Yugoslavia .....
☒ **ZA** South Africa .....
☒ **ZW** Zimbabwe .....

Check-box reserved for designating States which have become party to the PCT after issuance of this sheet:

☐ .....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) (22.11.1999) 22 November 1999	9904222-8	Sweden		
item (2)				
item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): (1)

* *Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)*: ISA / SE

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority)*:

Date (day/month/year)	Number	Country (or regional Office)
12 July 2000	ITS SE99/01536	Sweden

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets**:

request	: 3
description (excluding sequence listing part)	: 23
claims	: 5
abstract	: 1
drawings	:
sequence listing part of description	:
Total number of sheets	: 32

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Södertälje, 16 November 2000

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Britta Samuelsson
Global Intellectual Property, Patents, AstraZeneca AB

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(54) Title: NEW FUNCTIONALIZED POLYMERIC REAGENTS

(57) Abstract: The present invention relates to functionalized polymeric reagents useful in solution and solid-phase synthesis. It relates more specifically to functionlized polymeric reagent, comprising an acid labile isonitrile moiety. In further aspects the present invention also relates to use of such functionalized polymeric reagent in solution and solid-phase synthesis, a method for preparing an organic compound by solution and solid-phase synthesis using such functionalized polymeric reagent, a method for preparing such functionalized polymeric reagent and to kits comprising the functionalized polymeric reagent of the invention. The present invention also relates to new intermediates for use in the preparation of the novel functionalized polymeric reagent. In one aspect, the present invention provides a functionalized polymeric reagent for use in solution and solid-phase synthesis, e.g. multicomponent reactions. The functionalized polymeric reagent comprises a linker, and said linker comprises an acid labile isonitrile moiety. The linker is covalently attached to the polymeric support.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

IPC7: B01J 19/00, C07C 265/08
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07C, B01J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chem. Ber., Volume 111, 1978, Giselher Skorna et al, "Bifunktionelle Isocyanide als Reagenzien zur Einführung von Isocyangruppen in Polystyrol-Divenylbenzol-Copolymere" page 3965 - page 3968	1
A	--	2-5
X	Tetrahedron Letters, Volume 38, No 3, 1997, Kevin M. Short et al, "A Solid-Phase Combinatorial Method for the Synthesis of Novel 5-and 6-Membered Ring Lactams" page 359 - page 362	1
A	--	2-15

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/02263

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Tetrahedron Letters, Volume 39, 1998, Christopher Hulme et al, "Novel Safety-Catch Linker and its Application with a Ugi/De-BOC/Cyclization (UDC) Strategy to access Carboxylic acids 1,4-Benzodiazepines, Diketopiperazines Ketopiperazines and Dihydroquinoxalinones" page 7227 - page 7230	1-15
A	Tetrahedron Letters, Volume 39, 1998, Christopher Hulme et al, "The Solution Phase Synthesis of Diketopiperazine Libraries via the Ugi Reaction: Novel Application of Armstrong's Convertible Isonitrile" page 1113 - page 1116	1-15
A	Int. J. Peptide Protein Res., Volume 36, 1990, Jun Shao, You-He Li et al, "Acid labile anchoring linkages for solid phase synthesis of C-terminal asparagine peptides using the Fmoc strategy" page 182 - page 187	1-15
A	US 4812532 A (MARK L. STOLOWITZ), 14 March 1989 (14.03.89)	1-15
A	WO 9925752 A1 (RHONE-POULENC RORER PHARMACEUTICALS INC.), 27 May 1999 (27.05.99)	1-15
P,A	Publication Number AAT 9964314, Binet, Sopie Marie: "Design of new isonitriles for the asymmetric Ugi reaction application to the synthesis of an unique vinyl fluoride peptide isostere and to the synthesis of small heterocyclic molecules"; ISBN: 0-599-68736-3, Source: DAI-B 61/03, p. 1410, Sep 2000, abstract	1-15

INTERNATIONAL SEARCH REPORT

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PCT/SE 00/02263

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, wher appropriate, of the relevant passages	Relevant to claim No.
P,A	Tetrahedron Letters, Volume 41, 2000, Stefano Maiorana et al, "New polymer-bound haloarene chromium dicarbonyl isocyanide complexes: a successful study validating their use in solid-phase chemistry" page 7271 - page 7275 --	1-15
P,A	ABSTRACTS OF PAPERS, Part 2, 219th ACS National Meeting, 0-8412-3731-X, American Chemical Society, San Francisco, CA, March 26-30, 2000, Abstracts no: 125 New "Convertible" Isonitriles For The Ugi Reaction", Russell J Linderman et al -- --------	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internati nal application No.
PCT/SE 00/02263

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4812532 A	14/03/89	NONE	
WO 9925752 A1	27/05/99	AU 1589099 A	07/06/99
		US 6127515 A	03/10/00

Applicant: **AstraZeneca AB**
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Title: **NEW FUNCTIONALIZED POLYMERIC REAGENTS**

Reference: H 2272-1 WO

Inventors: Patrick Page

NEW FUNCTIONALIZED POLYMERIC REAGENTS

TECHNICAL FIELD

The present invention relates to polymer supports useful in solution and solid-phase synthesis. It relates more specifically to functionalized polymeric reagents, comprising an acid labile isonitrile moiety. In further aspects the present invention also relates to use of such functionalized polymeric reagents in solution and solid-phase synthesis, a method for preparing an organic compound by solution or solid-phase synthesis using such functionalized polymeric reagents, a method for preparing such functionalized polymeric reagents and to kits comprising the functionalized polymeric reagenta according to the invention. The present invention also relates to new intermediates for use in the preparation of the novel functionalized polymeric reagents.

BACKGROUND ART

The use of solid-phase synthesis for the synthesis of organic compounds has received a lot of attention lately. The reason for this is that solid-phase synthesis has several advantages compared to traditional solution-phase synthesis. Examples of such advantages include the ease with which products can be separated and purified from excess reagents by a simple washing step and the rapid isolation of product when cleaved and washed from the polymeric support.

The concomittant evolution of combinatorial chemistry and the improvement in automated syntheses has put a bonus on functionalized polymeric reagent. Combinatorial chemistry, combined with High Throughput Screening has revolutionized the speed with which the pharmaceutical industry can produce and screen compounds.

A prerequisite for solid-phase synthesis is a functionalized and stable polymeric support. Many of the commercially available polymeric supports have been developed for solid-

phase peptide synthesis and are therefore not inevitably suitable for solid-phase synthesis of compounds with non-peptidic structures.

Although highly successful, solid-phase synthesis exhibits several shortcomings due to the nature of heterogeneous reaction conditions, of which non-linear kinetic behavior is one. By replacing insoluble polymers, such as cross-linked polystyrene, with soluble polymers, such as PEG, the familiar reaction conditions of classical organic chemistry is reinstated, and yet product purification is still facilitated through application of macromolecular properties. This methodology in essence avoids the difficulties of solid-phase synthesis while preserving its positive aspects.

A key step in the synthesis of libraries of non-peptidic structures, or other biological active compounds in general, is to find the shortest synthetic pathway in order to speed up the chemistry optimization and production phase. One alternative is to use multicomponent reactions involving at least 3 reactants, which directly gives the product in a very efficient process. Several multicomponent reactions (MCR) have been described in the literature and one of the most widely utilized is the Ugi MCR. Multicomponent reactions can be performed either in solution or on solid phase. Although the solution phase alternative has proven its efficiency for the synthesis of a large number of biological compound, its major drawback is the need of purification steps in order to remove the excess of starting materials. This slows down the overall production process and/or limits its appropriateness for automated or semi-automated synthesis.

One commercially available functionalized polymeric reagent comprising an isonitrile moiety is shown below in Figure 1. The isonitrile moiety can not be cleaved from the polymeric support by acid treatment.

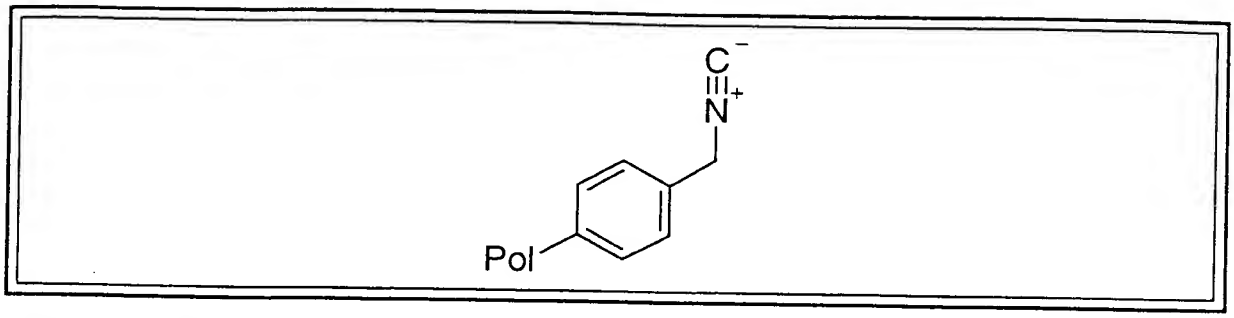


Figure 1. Commercially available functionalized polymeric reagent containing an isonitrile moiety

This drawback is overcome by the present invention, which thereby introduces a novel use for functionalized polymeric reagents comprisingan isonitrile moiety. Isonitriles have always been a poor source of diversity in combinatorial chemistry. This is due to the low number of commercially available isonitriles and the cost associated with time-consuming efforts of custom syntheses of a large number of diverse isonitriles. The present invention overcomes these problems by use of a resin capture strategy where the reactive isonitrile moiety is attached to the polymeric support in such a way as to make it cleavable by acid. The resin capture strategy used has a further advantage in that it gives no by-products that are fragments of the desired final product. Compounds synthesized by this resin capture strategy and released by acid cleavage are pure and do not require any further purification steps.

SUMMARY OF THE INVENTION

The present invention provides a functionalized polymeric reagent comprising a linker moiety for use in solution and solid-phase synthesis. The linker is compatible with a number of reagents and reaction conditions used in the synthesis of organic compounds. The functionalized polymeric reagent is also useful in combinatorial chemistry.

Thus, one aspect of the present invention is a functionalized polymeric reagent for use in solution and solid-phase synthesis. The functionalized polymeric reagent comprises a

linker, and said linker comprises an acid labile isonitrile moiety. The linker is covalently attached to the polymeric support.

In another aspect the present invention provides a method for preparing an organic compound by solution or solid-phase synthesis. The method comprises the step of immobilizing a substrate compound on the polymeric support via said isonitrile moiety. The thereby attached substrate compound is thereafter taken through at least one further organic reaction step to produce the desired compound, which is thereafter cleaved from the polymeric support and isolated. In a preferred embodiment, said method is performed with a variegated population of substrates and/or a plurality of organic reactions to provide a library of organic compounds.

In another aspect the present invention provides a method for preparing an organic compound by solution or solid-phase synthesis. The method comprises the step of a multi-component reaction being performed on the acid labile isonitril moiety of the functionalized polymeric reagent. In a preferred embodiment the multi-component reaction is an Ugi or an Ugi-type reaction.

In another aspect the present invention provides a method for preparing a functionalized polymeric reagent. The method comprises the step of reacting a suitable polymeric support comprising an amino group with a "formylating" reagent. The thereby produced formamido group is thereafter converted to an isonitrile moiety. In a preferred embodiment the amino group is treated with 2,4,5-trichlorophenylformate in DMF and the resulting formamido group is treated with triphenylphosphine / carbon tetrachloride and triethylamine in dichloromethane.

In another aspect the present invention provides new intermediates for use in the preparation of the novel functionalized polymeric reagents.

Accordingly, it is an object of the present invention to provide a functionalized polymeric reagent for use in solution or solid-phase synthesis.

It is another object of the present invention to provide a method for preparing an organic compound by solution or solid-phase synthesis.

It is another object of the present invention to provide a method for preparing a library of organic compounds.

It is another object of the present invention to provide a method for preparing a functionalized polymeric reagent.

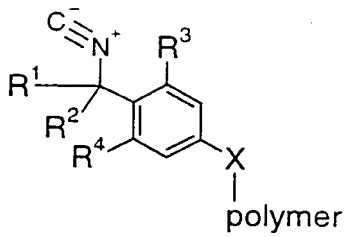
It is another object of the present invention to provide a new intermediate for use in the preparation of a functionalized polymeric reagent.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to functionalized polymeric reagents suitable for solution and solid-phase synthesis, to preparation of said functionalized polymeric reagents, and to use of said functionalized polymeric reagents in solution and solid-phase synthesis of organic compounds, including libraries.

In one aspect, the present invention provides a functionalized polymeric reagent for use in solution and solid-phase synthesis. The functionalized polymeric reagent comprises a polymeric support and an acid labile isonitrile moiety , wherein said polymeric support comprises a polymer and a linker. The linker is covalently attached to the polymer and the isonitrile moiety is covalently attached to the linker.

Preferred functionalized polymeric reagents of the present invention are those of Formula I



(I)

wherein

X is oxygen, a PEG-chain or a $-(CH_2)_n$-CONH- group,

R^1 is carbon, hydrogen, phenyl, or substituted phenyl group,

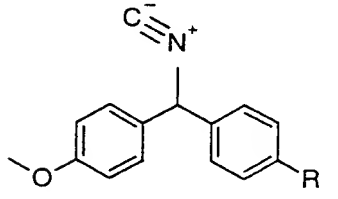
R^2 is hydrogen, phenyl, or substituted phenyl group

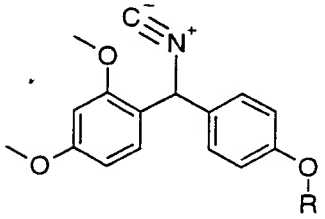
R^3 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or phenoxy,

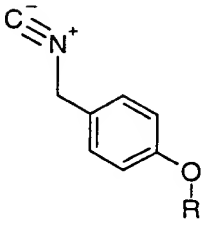
R^4 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or phenoxy, and

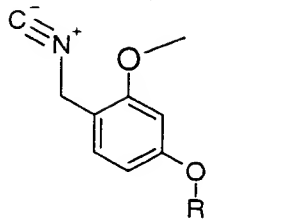
n is an integer from 1 to 4.

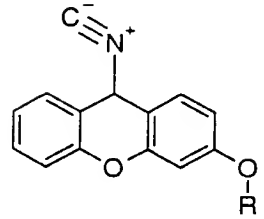
More preferred functionalized polymeric reagents of the present invention are

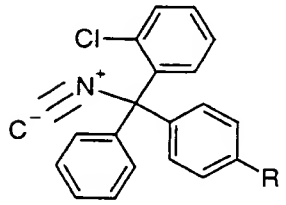












wherein R is a polymer directly attached to the linker or through a PEG-chain or a –$(CH_2)_n$-CONH- group.

The following definitions shall apply throughout the specification and the appended claims:

The term " functionalized polymeric reagent" denotes a reagent that is covalently attached to a linker moiety, and said linker is covalently attached to a polymer.

The term "polymeric support" denotes a polymer covalently attached to a linker moiety, which can optionally further be attached to a substrate compound.

The term "linker" denotes a reactive functional group that can be used to link molecules onto polymeric supports.

The term "acid labile isonitrile" denotes an isonitrile moiety which is cleaved from the linker when treated with aqueous trifluoroacetic acid (95%) at room temperature with a half time of less than 30 minutes.

The term "substrate compound" denotes a compound to be modified in a subsequent reaction step.

The term "immobilize" denotes the act of linking, *e.g.* a substrate compound, by means of chemical or biological procedure to a polymeric support.

The term "multicomponent reaction" denotes a one-pot reaction that form products from at least three different starting materials and incorporate substantial portions of these reagents into the product. This includes reactions involving at lest three different functional groups, some of which may be parts of the same reagent molecule.

The term "variegated population" denotes a population including at least two different chemical entities, e.g., of different chemical structure. For example, a "variegated population" of nucleophiles would comprise at least two different nucleophiles.

The term "substituted phenyl" denotes a phenyl group substituted with at least one of the following; C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, or phenoxy group.

The term "formylating reagent" denotes a reagent that can convert an amino group into a formamido group.

Polymeric supports

The choice of the soluble or insoluble polymer of the polymeric support is not crucial. Suitable soluble and insoluble polymers therefore consists of those known to the skilled artisan in the art of solution or solid-phase synthesis. Examples of suitable insoluble polymer include, but is not limited to, inorganic substrates, *e.g.* kieselguhr, silica gel and controlled pore glass, and polymeric organic substrates, *e.g.* polystyrene, polypropylene, polyethylene glycol, , as well as composite inorganic/polymeric substrates such as polyacrylamide supported within a matrix of kieselguhr particles. Preferred insoluble polymers are 1% DVB polystyrene and polystyrene-PEG.

Examples of suitable soluble polymers include, but is not limited to, polystyrene (not cross-linked, polyvinyl alcohol, polyethylene imine, polyacrylic acid, polymethylene oxide, PEG, polypropylene oxide, cellulose, polyacrylamide, PEG with 3,5-diisocyanatobenzyl chloride, PEG with 3-nitro-3-azapentane 1,5-diisocyanate, polyvinyl

alcohol-poly(1-vinyl-2-pyrrolidinone, polystyrene-poly(vinyl-substituted monosaccharides), poly(N-isopropylacrylamide)-poly(acrylic acid derivatives).

By replacing insoluble polymers with soluble polymers the familiar reaction conditions of classical organic chemistry is reinstated, and yet product purification is still facilitated through application of macromolecular properties. The present invention thereby avoids the difficulties of solid-phase synthesis while preserving its positive aspects.

Linkers

The choice of the linker is not limited to MAMP resin (amino-(4-methoxyphenyl)methyl polystyrene) (A), and therefore also includes, but is not limited to, Rink amide (B), Wang amino (C), Sasrin amino (D), Sieber amide (E) and 2-chlorotrityl linker (F) shown in Figure 2 below.

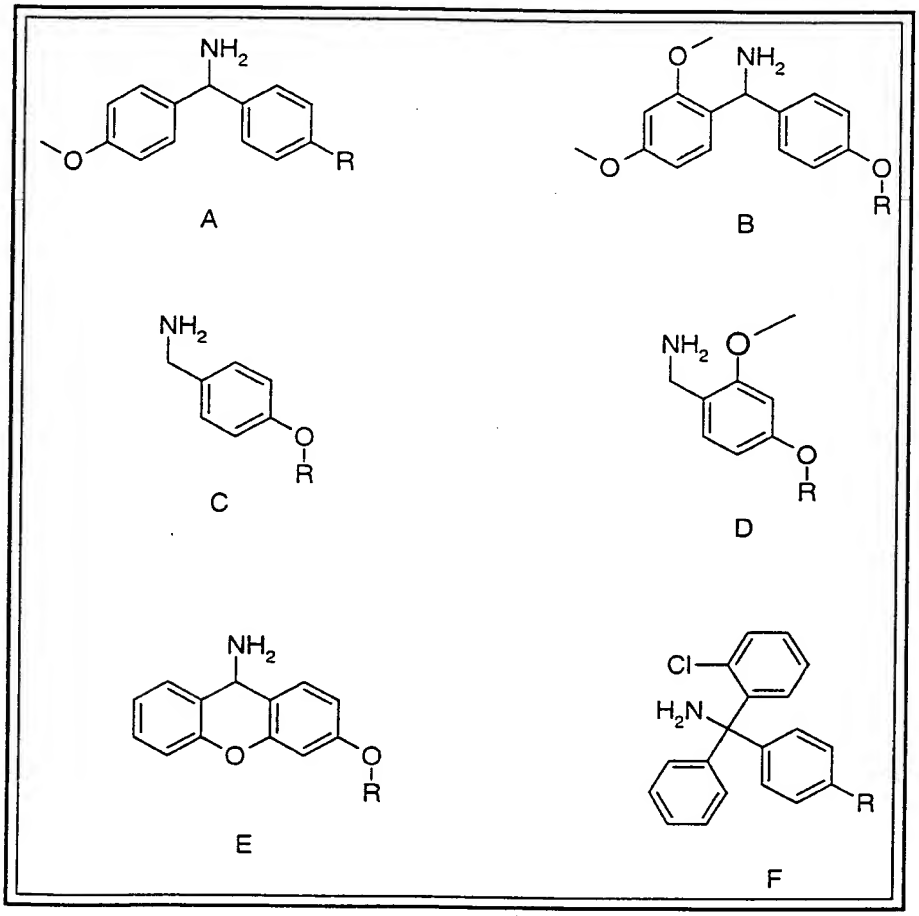


Figure 2. Linkers

In figure 2, R represents the polymeric support either directly attached to the linker or through a spacer moiety, such as a PEG-chain or a $-(CH_2)_n$-CONH- group.

Preparation of Functionalized Polymeric Reagents

A simple synthesis of a functionalized polymeric reagent is schematically shown in Figure 3 and described in more detail in Example 1.

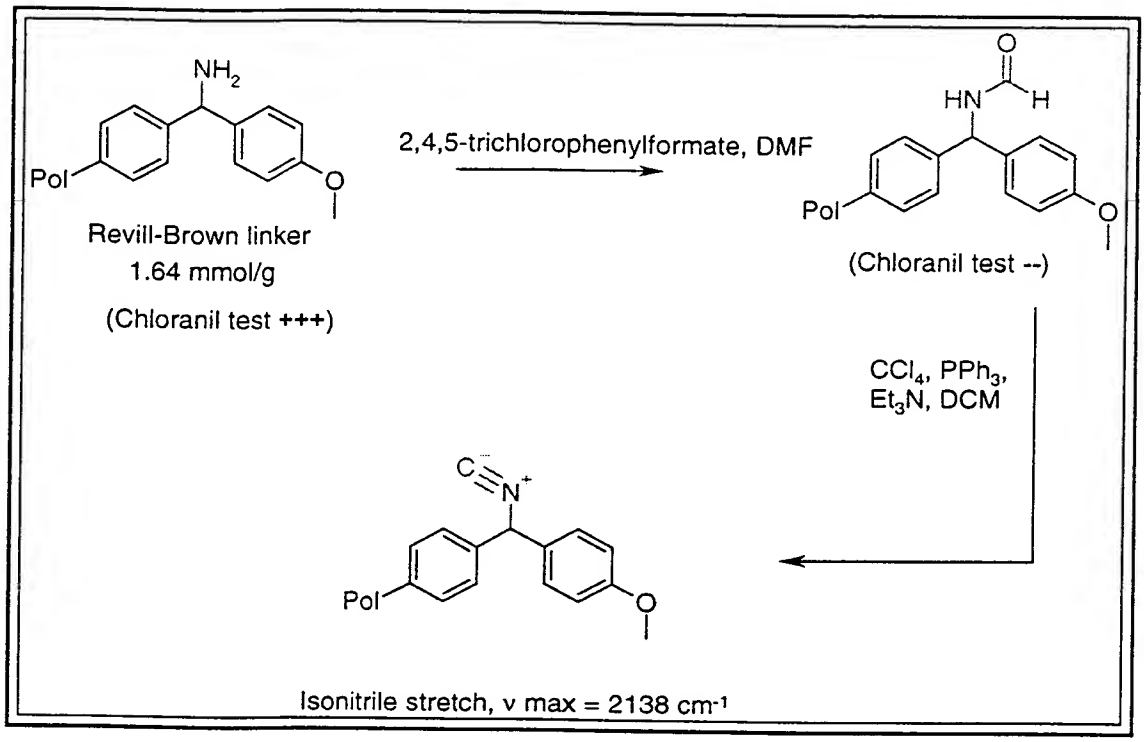


Figure 3. Synthesis of a Functionalized Polymeric Reagent

In this example, the functionalized resin is prepared by mixing a polymeric support (for example, amino MAMP linker 100-200 mesh or 200-400 mesh, commercially available from Novabiochem) in a polar solvent (*e.g.*, DMF) with a suitable "formylating" reagent, *e.g.* 2,4,5-trichlorophenylformate, as shown in figure 3. The reaction can be performed at room temperature or, in certain embodiments, at elevated temperature to ensure completeness of reaction and/or to decrease reaction times. The time required for the reaction can range from about 3 hours to 24 hours or more; an exemplary reaction time is 12 hours at room temperature.

The formed formamido intermediate is thereafter reacted at room temperature with carbon tetrachloride (CCl_4) / triphenylphosphine (PPh_3) in a non-polar solvent, *e.g.* dichloromethane (DCM) for approximately 3 hours in the presence of a base, *e.g.* triethylamine (Et_3N) to give the corresponding isonitrile.

This procedure has the advantage that is requires only a minimum number of synthetic steps, uses readily available reagents, and provides a functionalized polymeric reagent in good yield with simple purification steps.

Completeness of reaction with the functionalized polymeric reagent or polymeric supportcan be assessed according to standard techniques such as microanalysis, spectroscopic analysis, or by colorimetric tests. For example, the formation of an isonitril moiety can be monitored by Fourier-transform infra-red spectroscopy (FT-IR), e.g., by monitoring the isonitril stretch at 2138 cm^{-1}. Once the reaction has reached a pre-selected endpoint, the resin is preferably purified by washing. To ensure removal of excess reagents, several cycles of washing, preferably with solvents of a variety of polarities, can be carried out.

Once the functionalized polymeric reagent or polymeric support has been prepared and washed it is stable at room temperature for long periods of time. The functionalized polymeric reagent can be stored for extended periods of time without loss of activity.

Cleavage of Compounds from the Polymeric Support

It will be appreciated from the foregoing that the present invention provides a functionalized polymeric reagent, comprising an acid labile isonitrile moiety for use in solution and solid-phase synthesis. Compounds can be cleaved from the polymeric support with a variety of acids including, but not limited, to the following; TFA in DCM (20%), 4 M HCl in dioxane, HF, acetic acid in DCM (80%). A person skilled in the art can easily optimize the conditions to get the best possible result in the cleavage step. In general, the resin-bound compounds are preswollen in DCM for 10 min, the resin filtered and a solution of DCM:TFA:water (80:18:2) or 4M HCl in Dioxane was added and the reaction mixture was agitated for 1 hour at room temperature. The solution is filtered and evaporated to give the crude final compound.

Synthesis of Organic Compounds on the Polymeric Support

The present invention provides a method for synthesizing organic compounds by solution or solid-phase synthesis. In one embodiment, the method includes the steps of immobilizing a substrate compound on a polymeric support and at a later stage, cleaving the product from the polymeric support with an acid. As described in more detail below, in certain embodiments, the substrate compound is provided as a variegated population of substrate compounds, such that a library of organic compounds can be prepared.

Persons skilled in the art will appreciate that the immobilized substrate compound can be chemically manipulated while attached to the polymeric support. Thus, in certain embodiments, the method for synthesizing organic compounds by solution or solid-phase synthesis can include a plurality of further reaction steps, after the immobilizing step but before the cleaving step. Such synthetic manipulations include reactions, which are standard in solution and solid-phase synthesis. The reaction conditions for such manipulations will generally be selected to avoid cleavage of the substrate compound from the support, unless such concomitant cleavage is desired.

Combinatorial Chemistry on the Polymeric Support

Functionalized polymeric reagents of the present invention are suitable for use in combinatorial chemistry. Accordingly, in another aspect, the invention provides a method for the solution or solid-phase supported chemical synthesis of libraries. In one embodiment, the method comprises the step of reacting a substrate compound, which is immobilized on a polymeric support of the invention, with reagent molecules under conditions such that a library of compounds is prepared. In this embodiment, at least one of the substrate compound or the reagent molecule is provided as a variegated population thereof. It will be appreciated that the method can include the step of cleaving the library

of compounds from the polymeric support. Such a cleavage step can be concomitant with the reacting step, or, in certain embodiments, can be a separate cleavage step.

Combinatorial libraries can be screened to determine whether any members of the library have a desired activity, and, if so, to identify the active compounds. Soluble compound libraries can be screened by affinity chromatography with an appropriate receptor to isolate ligands for the receptor, followed by identification of the isolated ligands by conventional techniques (e.g., mass spectrometry, NMR, and the like). Contacting the compounds with a soluble receptor can screen immobilized compounds; preferably, the soluble receptor is conjugated to a label (e.g., fluorophores, calorimetric enzymes, radioisotopes, luminescent compounds, and the like) that can be detected to indicate ligand binding. Alternatively, immobilized compounds can be selectively released and allowed to diffuse through a membrane to interact with a receptor.

Combinatorial libraries of compounds can also be synthesized with "tags" to encode the identity of each member of the library. In general, this method features the use of inert, but readily detectable, tags that are attached to the solid support or to the compounds. When an active compound is detected (e.g., by one of the techniques described above), the identity of the compound is determined by identification of the unique accompanying tag. This tagging method permits the synthesis of large libraries of compounds that can be identified at very low levels.

A variegated population of substrate compounds can provide diversity in a combinatorial synthesis. Several methodologies have been developed to perform combinatorial chemistry. Examples of such methodologies include, but is not limited to, the mix and split technology and IRORI MiniKans.

Multicomponent Reactions on the Polymeric Support

The polymeric support of the invention is suitable for use with multicomponent reactions, but not limited to them. Multicomponent reactions have become increasing common and have been extensively reviewed see *e.g. Lutz Weber, Synlett 1999, no 3, 366-374; Kevin Short, Tetrahedron vol.53, no19, 6653-6679, 1997; Sang Kim, Tetrahedron Letters, 39 (1998) 6993-6996; Blacburn, Tetrahedron Letters (1998) 39, 5469-5472, Bienayme , Angew. Chem. Int. Ed. (1998) 37, no 16; Blackburn 39, (1998) 3635-3638 Tetrahedron Letters.*

In a multicomponent reaction three or more component molecules can react simultaneously or close to simultaneously with each other to provide a molecule which has incorporated substantial portions of these reagent molecule without any isolation of intermediates. This includes reactions involving at least three different functional groups, some of which may be parts of the same reagent molecule. In general a multicomponent reaction is sequences of bimolecular reaction steps that proceed according to the zipper principle, *i.e.* each reaction step is a prerequisite for the following step. Examples of multicomponent reactions include but are not limited to, α-aminoalkylation (Mannich), Passeriini, Ugi and Ugi-type. Ugi and Ugi-type reactions are preferred multicomponent reactions to be used with the polymeric supports of the present invention. Ugi and Ugi-type reactions give access to compounds and functionalities of great interest for a medicinal chemist, *e.g.* heterocyclic compounds.

Accordingly, in another aspect, the invention provides methods for the multicomponent synthesis of organic compounds. In one embodiment, the method comprises the step of reacting the isonitrile moiety with at least two reagent molecules simultaneously under conditions such that a multicomponent reaction is achieved.

A preferred embodiment of the present invention is schematically shown below in Figure 4.

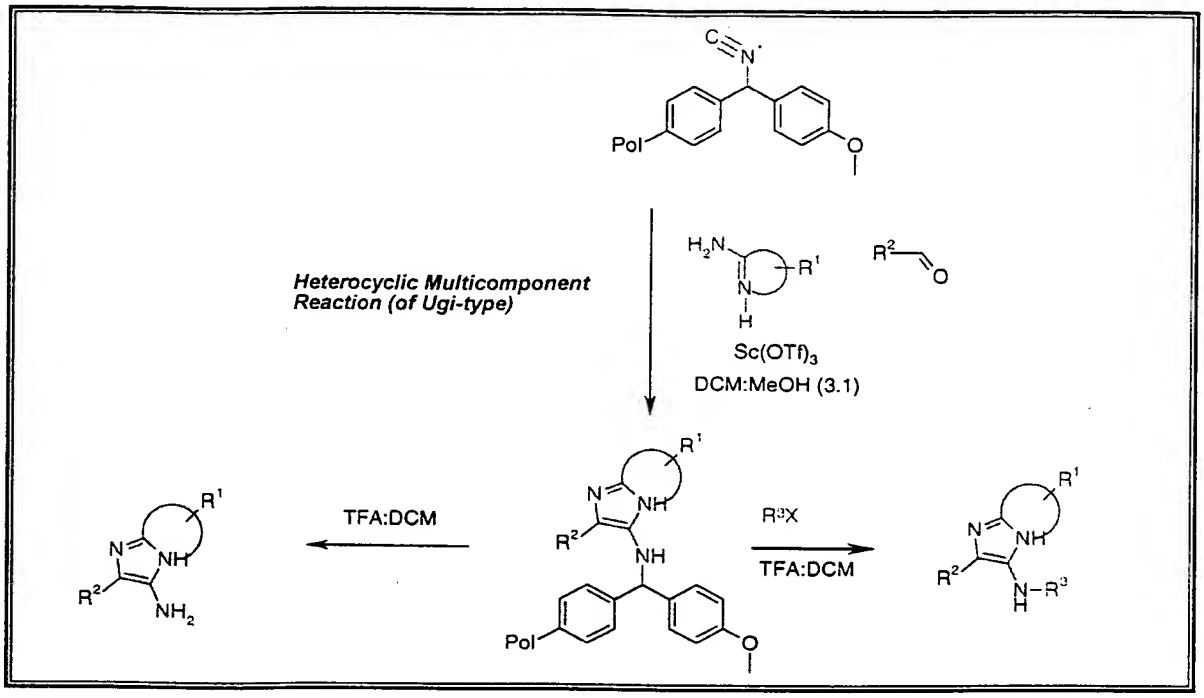


Figure 4. Heterocyclic Multicomponent Reaction

The preferred embodiment shown in Figure 4 is advantageous since it allows a multicomponent reaction to be performed directly onto the acid labile isonitrile moiety of the functionalized polymeric reagent.

The example outlined above consists of a multicomponent Ugi-type condensation wherein the isonitrile moiety of the functionalized polymeric reagent is reacted with 2 different source of diversity, aldehydes and heteroaromatic amidines. This Ugi-type reaction leads efficiently and in a one step process to the fused 3-aminoimidazoles, using the resin capture strategy. The final compounds are of high purity after acid cleavage.

3-aminoimidazoles has been synthesized according to the present invention. A wide range of aldehydes and heteroaromatic amidines was utilised to test the functionalized polymeric reagent and showed the efficiency of the resin capture by obtaining a high yield and excellent purity of the final products. Typical procedure for the synthesis of fused 3-aminoimidazoles by Ugi type reaction and resin capture strategy is described in Example 3, below.

The fused 3-aminoimidazoles contains a nitrogen atom, involved in an amine bond with the polymeric support, which can be further reacted with various electrophilic molecules, *e.g.* acyl halides, alkyl halides, or sulfonyl halides, and thereafter, be cleaved from the polymeric support. This tandem reaction process (MCR + acylation/alkylation) increases the diversity which can be introduced onto the 3-fused aminoimidazole core. The thereby introduced additional diversity is a further advantage of the present invention, since the access of these compounds by traditional solution-phase without polymeric support is cumbersome, since the corresponding isonitriles are either not commercially available or time-consuming to synthesize. Due to the low number of commercially available isonitriles able to be utilised in combinatorial chemistry (<20) and the cost and time-consumption of custom syntheses, the isonitriles have always been the poorest source of diversity involves in the Ugi reaction.

One of the advantages of the present invention is to overcome this kind of problem. The amino functionality of the aminoimidazoles can be utilised for further reactions, such as acylation or alkylation reactions. For example, acyl chlorides, sulfonyl chlorides or alkyl halides can be used as source of diversity and will enhance the diversity of the aminoimidazoles. The Tandem reaction concept by coupling a multi component reaction with an additional alkylation or acylation step makes the whole process highly efficient with respect to the final diversity of the aminoimidazoles synthesized. The present invention also have a postitive impact on the size and the speed by which a library can be generated. The tandem 3CC+1 strategy has enhanced the diversity of the fused 3-aminoimidazoles by using 3 non-exhaustive sources of diversity, *i.e.* acyl chlorides, alkyl halides and sulfonyl chlorides. The typical procedures for the synthesis of these compounds are described below in Example 3.

The polymeric support of the present invention can also be used in general organic chemistry manipulations, such as cycloaddition reactions, as a dehydrating agent or as a

scavenger, *e.g.* for the removal of alkyl halides, phosphines, acid chlorides, aldehydes and ketones.

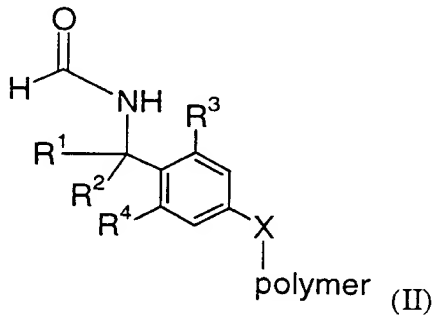
Kits

The present invention also provides a kit for use in solution and solid-phase synthesis. The kit includes a functionalized polymeric reagent of the present invention, *i.e.* for use in solution and solid phase chemistry, preferably in a container or package.

Intermediates

It is an object of the present invention to provide new intermediates for use in the preparation of the novel functionalized polymeric reagents.

Useful intermediates according to the present invention are compounds of Formula II



(II)

wherein

X is carbon, oxygen, a PEG-chain, or a $-(CH_2)_n$-CONH- group

R^1 is hydrogen, phenyl, or substituted phenyl group,

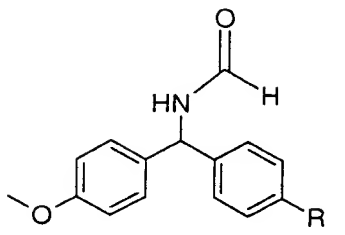
R^2 is hydrogen, phenyl, or substituted phenyl group,

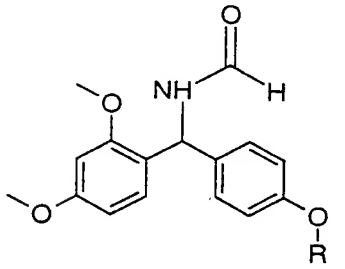
R^3 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or phenoxy,

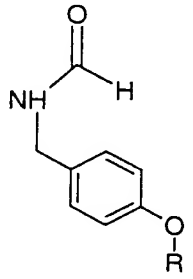
R^4 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or phenoxy, and

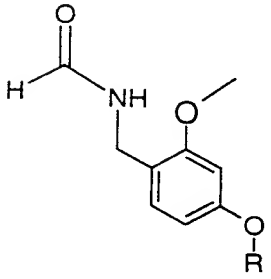
n is an integer from 1 to 4.

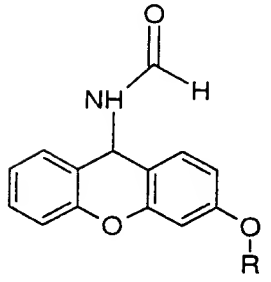
Preferred intermediates of the present invention are the following compounds;

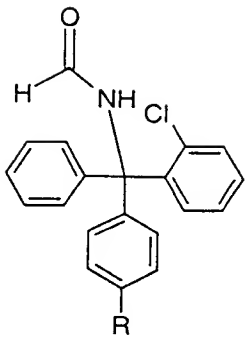












wherein, R represents the polymeric support either directly attached to the linker or through a spacer moiety, such as a PEG-chain or a $-(CH_2)_n$-CONH- group.

EXAMPLES

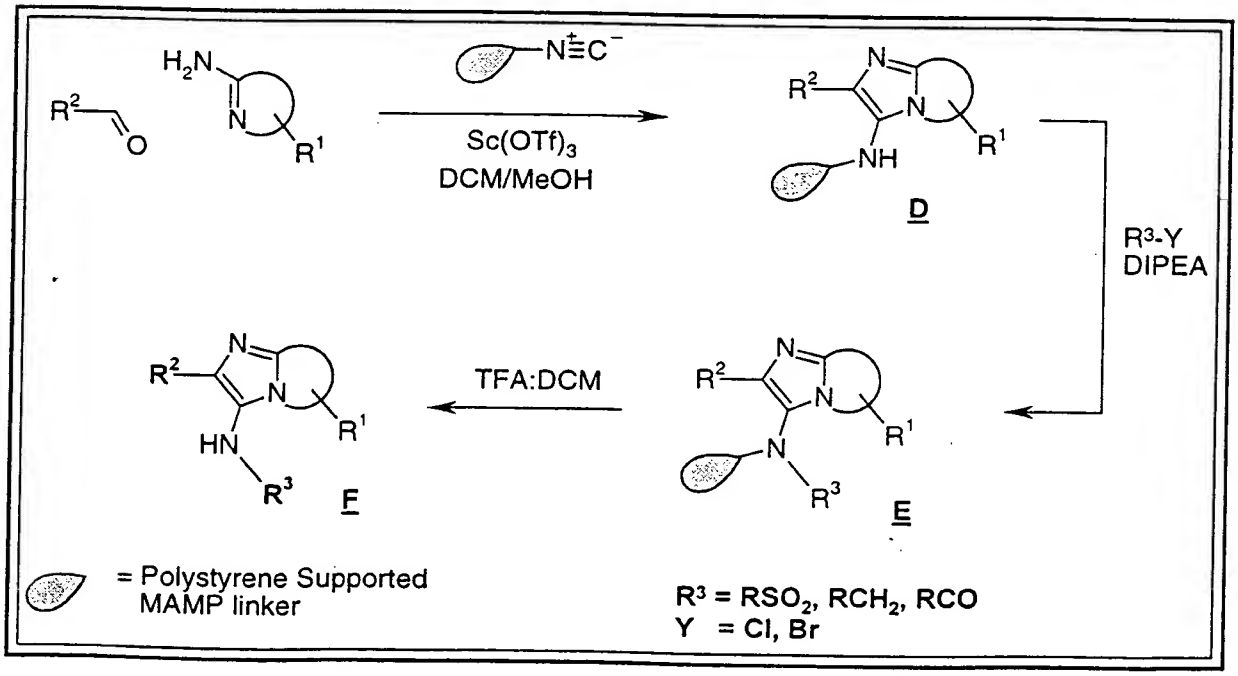
Example 1. Preparation of Functionalized Polymeric Reagent

The starting MAMP amino resin (1 gr; 1.64mmol/g) was pre-swollen in DMF for 10 minutes. To this resin was added a solution of 2,4,5-trichlorophenyl formate (560mg; 2.46mmol, 1.5eq) in 10 mL of DMF. The reaction mixture was agitated at room temperature for 12h. The resin was filtered and washed with DMF (2x10mL), DCM (2x10mL), MeOH (2x10mL) and finally dry under vacuum for 1 hour. The resin gives a negative chloranil test, which indicates completion of the reaction. The resin (1.64mmol) was thereafter washed with dry dichloromethane (2x10mL), pre-swollen in dry dichloromethane for 10 min, and filtered. A solution of triphenylphosphine (2.16g, 8.2mmol, 5eq), carbon tetrachloride (1.27g, 8.2mmol, 5eq) and triethylamine (830mg, 8.2mmol, 5eq) in dry dichloromethane 10mL was added followed by a few activated molecular sieves (4Å). The reaction mixture was shaken at room temperature for 3 hours. The resin was filtered, and washed with dichloromethane (2x10mL), methanol (2x10mL), and dichloromethane was added to afford the separation of the floating resin from the molecular sieves. The resin was washed with 10mL dichloromethane and diethyl ether

(2x10mL) and dried under vacuum for 12h. The resin was then kept under nitrogen at room temperature in the dark for 6 months without any modifcation of its efficiency.

Example 2. Resin Capture Strategy for the synthesis of fused 3-amino imidazoles.

The heteroaromatic amidine (323µmol, 200mol%), the aldehyde (323µmol, 200mol%) and the catalyst $Sc(OTf)_3$ (16.2µmol, 10mol%) in 1mL of a solution of DCM:MeOH (3:1) were incubated for 30min. The resin isonitrile linker (100mg, 163µmol, 100mol%) was preswollen for 20 minutes in DCM and the resin filtered. The solution of aldehyde, heteroaromatic amidines and catalyst was then added to the resin and the solution was shaken for 2 days at room temperature. The resin filtered and washed with DCM(2x3mL), MeOH(2x3mL), 20%DIPEA in DCM(3mL) and DCM(2x3mL). A sample of the resin (3-5mg) was cleaved from the resin with a solution DCM:4M HCl in dioxane(1:1) for 1h at room temperature. The residue was dried under vacuo and analysed by LC-MS, yielding the expected product in high purity (75-99%).



Scheme 1. Enhancement of diversity by reacting the nitrogen atom, involved in an amine bond with the polymeric support, *of the fused 3-aminoimidazole with various electrophiles.*

Exemple 3. Synthesis of amide substituted fused 3-aminoimidazoles

Resin-bound compound **D** (60mg, 74µmol, 100mol%) was preswollen in DCM for 20 minutes and the resin filtered. A solution of acyl chloride (370µmol, 500mol%) and DIPEA (600µmol, 800mol%) in 1mL of DCM was added to the resin-bound compound **D** and the reaction mixture was agitated for 20h at room temperature. The resin was filtered and washed with DCM (2x3mL), MeOH (2x3mL), and DCM(2x3mL). A sample of the resin (3-5mg) was cleaved from the resin with a solution of DCM:TFA:water (80:18:2) for 1h at room temperature. The residue was dried under vacuo and analysed by LC-MS, yielding the expected product in high purity (75-99%).

Exemple 4. Synthesis of alkylated 3-aminoimidazoles.

Resin-bound compound **D** (60mg, 74µmol, 100mol%) was preswollen in DMF for 20 minutes and the resin filtered. A solution of alkyl halides (370µmol, 500mol%) and DIPEA (740µmol, 1000mol%) in 1.2mL of DMF was added to the resin-bound compound **D** and the reaction mixture was agitated for 20h at 80°C. The resin was filtered and washed with DMF (2x3mL), DCM (2x3mL), MeOH (2x3mL), and DCM(2x3mL). A sample of the resin (3-5mg) was cleaved from the resin with a solution of DCM:TFA:water (80:18:2) for 1h at room temperature. The residue was dried under vacuo and analysed by LC-MS, yielding the expected product in high purity (75-99%).

Exemple 5. Synthesis of sulfonamide substituted 3-aminoimidazoles.

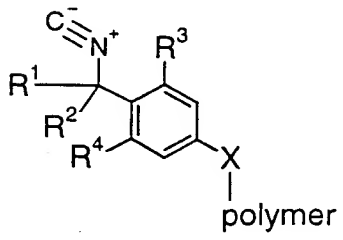
Resin-bound compound **D** (60mg, 74µmol, 100mol%) was preswollen in DCM for 20 minutes and the resin filtered. A solution of sulfonyl chlorides (370µmol, 500mol%) and DIPEA (740µmol, 1000mol%) in 1.2mL of DCM:Dioxane (1:1) was added to the resin-

bound compound **D** and the reaction mixture was agitated for 20h at 60°C. The resin was filtered and washed with DCM (2x3mL), Dioxane (2x3mL), MeOH (2x3mL), and DCM(2x3mL). A sample of the resin (3-5mg) was cleaved from the resin with a solution of DCM:TFA:water (80:18:2) for 1h at room temperature. The residue was dried under vacuo and analysed by LC-MS, yielding the expected product in high purity.

CLAIMS

1. A functionalized polymeric reagent for solution and solid-phase synthesis comprising a polymer and a linker moiety characterized in that the linker comprises an acid labile isonitrile moiety.

2. A functionalized polymeric reagent for solution and solid-phase synthesis of Formula I



(I)

wherein

X is carbon, oxygen, a PEG-chain, or a $-(CH_2)_n$-CONH- group,

R^1 is hydrogen, phenyl, or substituted phenyl group,

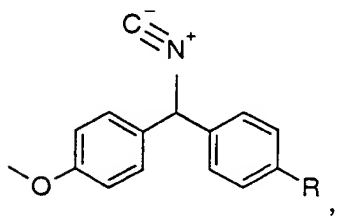
R^2 is hydrogen, phenyl, or substituted phenyl group,

R^3 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or phenoxy,

R^4 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or phenoxy, and

n is an integer from 1 to 4.

3. The functionalized polymeric reagent according to claims 1 or 2 being,



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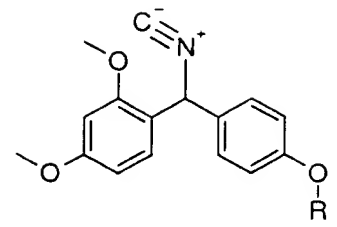
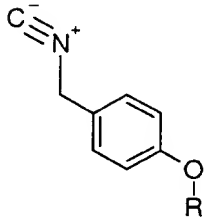
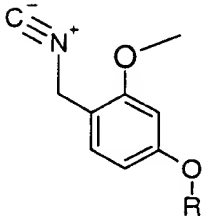
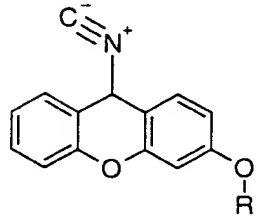
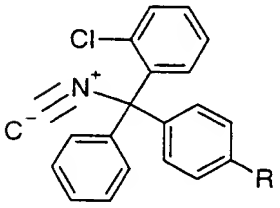










wherein R is a polymer directly attached to the linker or through a $-(CH_2)_n$-CONH- group,or a PEG-chain.

4. The functionalized polymeric reagent according to any of claims 1-3, characterized in that the polymer is a soluble polymer.

5. The functionalized polymeric reagent according to any of claims 1-3, characterized in that the polymer is an insoluble polymer.

6. A method for preparing a functionalized polymeric reagent according to claims 1-5, comprising the step of,

a) reacting the polymeric support with a formylating reagent;

b) converting the thereby formed formamido group into an isonitrile moiety.

7. The method according to claim 6, characterized in that the formylating reagent used in step a) is 2,4,5-trichlorophenyl formate.

8. The method according to claim 6 and 7, characterized in that the reagent used in step b) is carbon tetrachloride / triphenylphosphine in the presence of triethylamine.

9. A method for preparing an organic compound by solution and solid-phase synthesis comprising the steps of

a) immobilizing a substrate compound to the isonitrile moiety of the functionalized polymeric reagent according to claims 1-4

b) performing at least one further reaction step, and

c) cleaving the compound from the polymeric support by acid treatment.

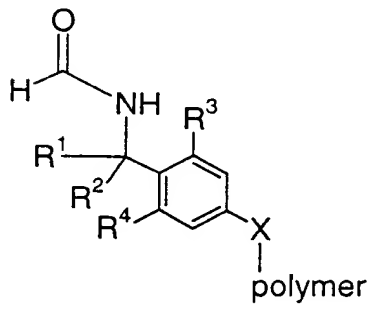
10. The method according to claim 9 comprising an additional reaction step after the cleavage from the polymeric support.

11. The method according to claim 9, characterized in that the method is performed with a plurality of substrate compounds and/or plurality of further reaction steps to give a library of organic compounds.

12. The method according to claim 9, characterized in that at least one of the reaction steps is a multicomponent reaction.

13. A kit comprising a container of a functionalized polymeric reagent according to claims 1-4.

14. Intermediate compounds of Formula II



(II)

wherein

X is carbon, oxygen, a PEG-chain, or a $-(CH_2)_n$-CONH- group,

R^1 is hydrogen, phenyl, or substituted phenyl group,

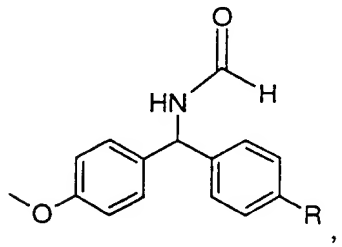
R^2 is hydrogen, phenyl, or substituted phenyl group,

R^3 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or phenoxy,

R^4 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or phenoxy, and

n is an integer from 1 to 4.

15. Compounds according to claim 13 being



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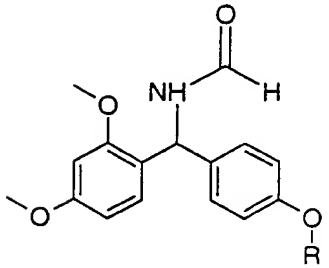

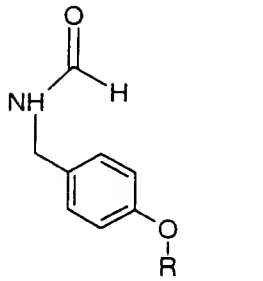

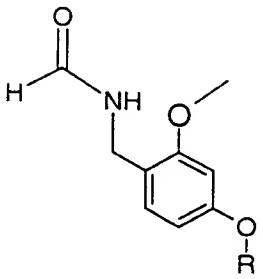

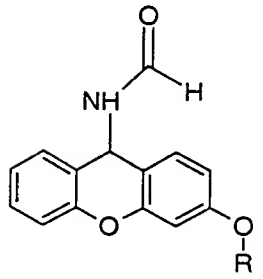

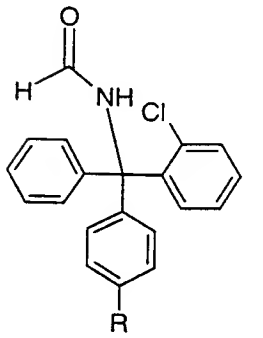

wherein, R represents the polymeric support either directly attached to the linker or through a spacer moiety, such as a PEG-chain or a $-(CH_2)_n$-CONH- group.

ABSTRACT

The present invention relates to functionalized polymeric reagents useful in solution and solid-phase synthesis. It relates more specifically to functionalized polymeric reagent, comprising an acid labile isonitrile moiety. In further aspects the present invention also relates to use of such functionalized polymeric reagent in solution and solid-phase synthesis, a method for preparing an organic compound by solution and solid-phase synthesis using such functionalized polymeric reagent, a method for preparing such functionalized polymeric reagent and to kits comprising the functionalized polymeric reagent of the invention. The present invention also relates to new intermediates for use in the preparation of the novel functionalized polymeric reagent. In one aspect, the present invention provides a functionalized functionalized polymeric reagent for use in solution and solid-phase synthesis, e.g. multicomponent reactions. The functionalized polymeric reagent comprises a linker, and said linker comprises an acid labile isonitrile moiety. The linker is covalently attached to the polymeric support.